

WHAT IS CLAIMED IS:

1. An oligomeric compound comprising a plurality of covalently-bound nucleosides said oligomeric compound having
5 an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking said internal region wherein said external regions impart nuclease resistance to said oligomeric compound.

2. The oligomeric compound of claim 1 wherein at least
10 one nucleoside in the external regions comprises a substituent group.

3. The oligomeric compound of claim 2 wherein at least one nucleoside in each of the external regions comprises a substituent group.

3. The oligomeric compound of claim 2 wherein each
15 nucleoside in the external regions comprises a substituent group.

4. The oligomeric compound of claim 2 wherein each of said substituent groups is covalently bound to the 5', 3' or
20 2'-position of the sugar moiety of said nucleoside.

5. The oligomeric compound of claim 4 wherein each of said substituent groups is covalently attached to said nucleoside at the 2'-position.

6. The oligomeric compound of claim 4 wherein each of
25 said substituent groups is covalently attached to said nucleoside at the 5'-position.

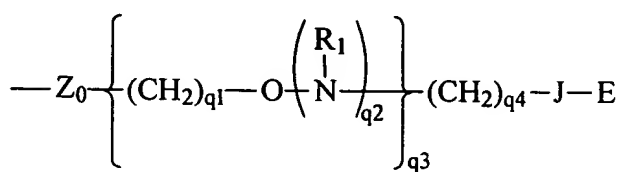
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7. The oligomeric compound of claim 1 wherein the ribosyl sugar moiety of at least one of said covalently-bound nucleosides in each of said external regions has the L-ribose configuration.

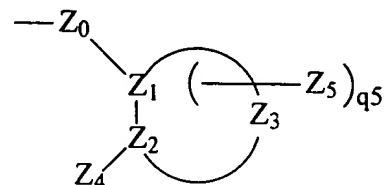
8. The oligomeric compound of claim 7 wherein the 5' and 3'-terminal ribosyl sugar moieties of said covalently-bound nucleosides each have the L-ribose configuration.

9. The oligomeric compound of claim 2 wherein each of said substituent groups is, independently, C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₅-C₂₀ aryl, O-alkyl, O-alkenyl, O-alkynyl, O-alkylamino, O-alkylalkoxy, O-alkylaminoalkyl, O-alkyl imidazole, thiol, S-alkyl, S-alkenyl, S-alkynyl, NH-alkyl, NH-alkenyl, NH-alkynyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, N-phthalimido, halogen, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, heterocycle, carbocycle, polyamine, polyamide, polyalkylene glycol, and polyether;

or each substituent group has one of formula I or II:



I



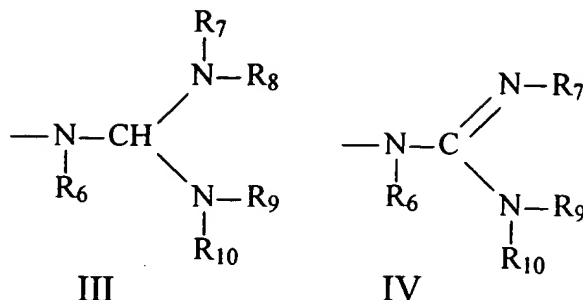
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wherein:

Z₀ is O, S or NH;

J is a single bond, O or C(=O);

E is C₁-C₁₀ alkyl, N(R₁)(R₂), N(R₁)(R₅), N=C(R₁)(R₂), N=C(R₁)(R₅) or has one of formula III or IV;



each R_6 , R_7 , R_8 , R_9 and R_{10} is, independently, hydrogen, $C(O)R_{11}$, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl, substituted or unsubstituted C_2 - C_{10} alkynyl, alkylsulfonyl, arylsulfonyl, a chemical functional group or a conjugate group, wherein the substituent groups are selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl;

- 10 or optionally, R_7 and R_8 , together form a phthalimido moiety with the nitrogen atom to which they are attached;
or optionally, R_9 and R_{10} , together form a phthalimido moiety with the nitrogen atom to which they are attached;

each R_{11} is, independently, substituted or unsubstituted C_1 - C_{10} alkyl, trifluoromethyl, cyanoethoxy, methoxy, ethoxy, t-butoxy, allyloxy, 9-fluorenylmethoxy, 2-(trimethylsilyl)-ethoxy, 2,2,2-trichloroethoxy, benzyloxy, butyryl, isobutyryl, phenyl or aryl;

R_5 is T-L,

- 20 T is a bond or a linking moiety;

L is a chemical functional group, a conjugate group or a solid support material;

each R_1 and R_2 is, independently, H, a nitrogen protecting group, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl, substituted or unsubstituted C_2 - C_{10} alkynyl, wherein said substitution is OR_3 , SR_3 , NH_3^+ , $N(R_3)(R_4)$, guanidino or acyl where said acyl is an acid amide or an ester;

or R_1 and R_2 , together, are a nitrogen protecting group or are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

or R_1 , T and L, together, are a chemical functional
5 group;

each R_3 and R_4 is, independently, H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_3 and R_4 , together, are a nitrogen protecting group;

or R_3 and R_4 are joined in a ring structure that
10 optionally includes an additional heteroatom selected from N and O;

Z_4 is OX, SX, or $N(X)_2$;

each X is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, $C(=NH)N(H)R_5$, $C(=O)N(H)R_5$ or $OC(=O)N(H)R_5$;

15 R_5 is H or C_1 - C_8 alkyl;

Z_1 , Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur and wherein said
20 ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14
25 carbon atoms, $N(R_1)(R_2)OR_1$, halo, SR_1 or CN;

each q_1 is, independently, an integer from 1 to 10;

each q_2 is, independently, 0 or 1;

q_3 is 0 or an integer from 1 to 10;

q_4 is an integer from 1 to 10;

30 q_5 is from 0, 1 or 2; and

provided that when q_3 is 0, q_4 is greater than 1.

10. The oligomeric compound of claim 9 wherein said substituent group has formula I, II, III or IV.

11. The oligomeric compound of claim 1 wherein at least one internucleoside linkage in one of said external regions is modified.

12. The oligomeric compound of claim 11 wherein at least
5 one internucleoside linkage in each of said external regions is modified.

13. The oligomeric compound of claim 11 wherein each of the internucleoside linkages in said external regions are modified.

10 14. The oligomeric compound of claim 11 wherein each modified internucleoside linkage is, independently, methyl phosphonate, boranophosphonate, phosphoramidate, 3'-methylenephosphonate or methylene(methylimino).

15 15. The oligomeric compound of claim 1 wherein at least one internucleoside linkage in one of said external regions is a 2', 5'-internucleoside linkage.

16. The oligomeric compound of claim 15 wherein at least one internucleoside linkage in each of said external regions
20 is a 2', 5'-internucleoside linkage.

17. The oligomeric compound of claim 1 comprising from 5 to about 50 nucleosides.

18. The oligomeric compound of claim 1 comprising from 8 to about 30 nucleosides.

25 19. The oligomeric compound of claim 1 comprising from 15 to about 25 nucleosides.

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20. The oligomeric compound of claim 1 wherein each of the external regions comprises from 1 to 6 nucleosides.

21. The oligomeric compound of claim 1 wherein each of the external regions comprise from 1 to 3 nucleosides.

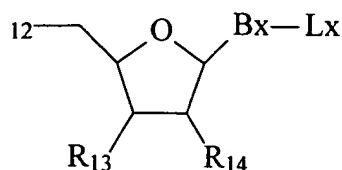
22. A pharmaceutical composition comprising a compound of claim 1 and an acceptable pharmaceutical carrier.

23. An oligomeric compound of the formula:



wherein:

each Nu_1 and Nu_2 , independently, has the formula:



wherein

Bx is a heterocyclic base moiety;

Lx is hydrogen, a protecting group or a substituent group;

one of R_{12} , R_{13} and R_{14} is hydroxyl, a protected hydroxyl, a covalent attachment to a solid support, a nucleoside, an oligonucleoside, a nucleotide, an oligonucleotide, a conjugate group or an optionally protected substituent group;

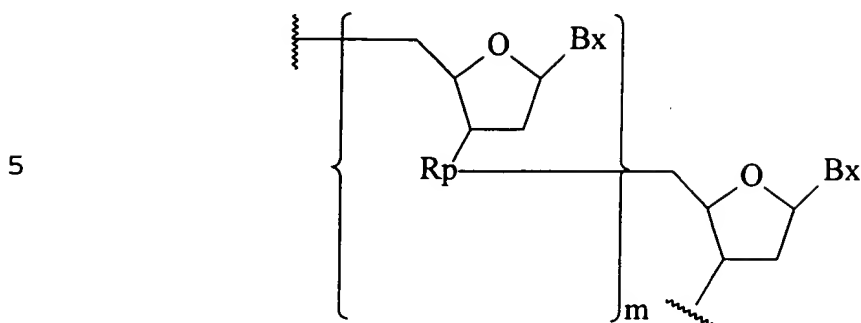
another of R_{12} , R_{13} and R_{14} is hydrogen, hydroxyl, a protected hydroxyl or an optionally protected substituent group;

the remaining of R_{12} , R_{13} and R_{14} , of Nu_1 , is L_1 ;

the remaining of R_{12} , R_{13} and R_{14} , of Nu_2 , is L_2 ;

each L_1 and each L_2 is, independently, a phosphodiester internucleoside linkage or a modified internucleoside linkage;

Y has the formula:



wherein:

each R_p is a chiral R_p phosphorothioate internucleotide linkage; and

10 each n, m and p is, independently, from 1 to 100; where
the sum of n, m and p is from 3 to about 200;

with the proviso that at least one of R_{12} , R_{13} , R_{14} and L_x is a substituent group or at least one of L_1 and L_2 is a modified internucleoside linkage.

15 24. The oligomeric compound of claim 23 wherein at least
one Nu₁ or at least one Nu₂ comprises a substituent group.

25. The oligomeric compound of claim 24 wherein at least one Nu₁ and at least one Nu₂ independently comprise a substituent group.

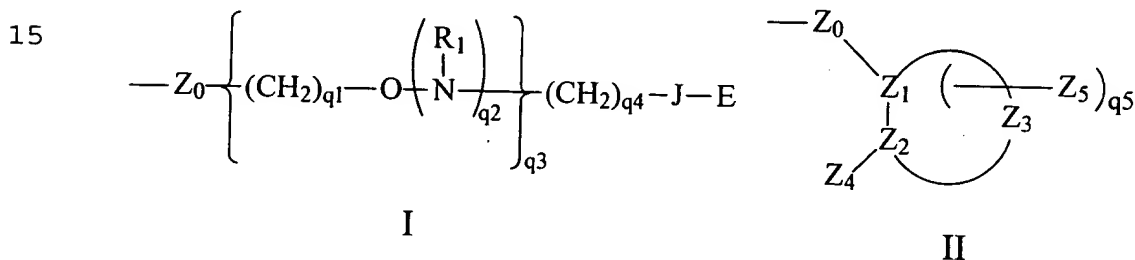
20 26. The oligomeric compound of claim 23 wherein each Nu₁
and each Nu₂ independently comprises a substituent group.

27. The oligomeric compound of claim 24 wherein said substituent group is covalently attached to the 2', 3' or 5'-position of said Nu₁ or Nu₂.

25 28. The oligomeric compound of claim 27 wherein said
substituent group is covalently attached to the 2'-position of
said Nu₁ or Nu₂.

29. The oligomeric compound of claim 23 wherein each of said substituent groups is, independently, C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₅-C₂₀ aryl, O-alkyl, O-alkenyl, O-alkynyl, O-alkylamino, O-alkylalkoxy, O-alkylaminoalkyl, O-alkyl imidazole, thiol, S-alkyl, S-alkenyl, S-alkynyl, NH-alkyl, NH-alkenyl, NH-alkynyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, N-phthalimido, halogen keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, heterocycle, carbocycle, polyamine, polyamide, polyalkylene glycol, and polyether;

or each substituent group has one of formula I or II:

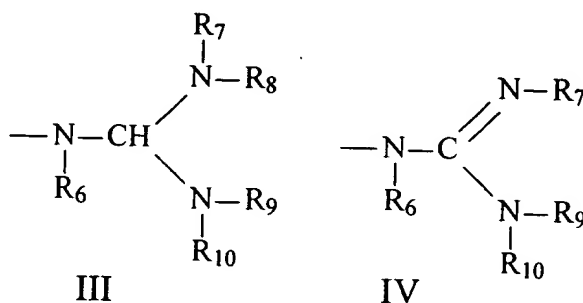


wherein:

Z₀ is O, S or NH;

J is a single bond, O or C(=O);

20 E is C₁-C₁₀ alkyl, N(R₁)(R₂), N(R₁)(R₅), N=C(R₁)(R₂), N=C(R₁)(R₅) or has one of formula III or IV;



each R₆, R₇, R₈, R₉ and R₁₀ is, independently, hydrogen, C(O)R₁₁, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl, substituted or unsubstituted

C₂-C₁₀ alkynyl, alkylsulfonyl, arylsulfonyl, a chemical functional group or a conjugate group, wherein the substituent groups are selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, 5 aryl, alkenyl and alkynyl;

or optionally, R₇ and R₈, together form a phthalimido moiety with the nitrogen atom to which they are attached;

or optionally, R₉ and R₁₀, together form a phthalimido moiety with the nitrogen atom to which they are attached;

10 each R₁₁ is, independently, substituted or unsubstituted C₁-C₁₀ alkyl, trifluoromethyl, cyanoethoxy, methoxy, ethoxy, t-butoxy, allyloxy, 9-fluorenylmethoxy, 2-(trimethylsilyl)-ethoxy, 2,2,2-trichloroethoxy, benzyloxy, butyryl, iso-butyryl, phenyl or aryl;

15 R₅ is T-L,

T is a bond or a linking moiety;

L is a chemical functional group, a conjugate group or a solid support material;

each R₁ and R₂ is, independently, H, a nitrogen protecting 20 group, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl, substituted or unsubstituted C₂-C₁₀ alkynyl, wherein said substitution is OR₃, SR₃, NH₃⁺, N(R₃)(R₄), guanidino or acyl where said acyl is an acid amide or an ester;

25 or R₁ and R₂, together, are a nitrogen protecting group or are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

or R₁, T and L, together, are a chemical functional group;

each R₃ and R₄ is, independently, H, C₁-C₁₀ alkyl, a 30 nitrogen protecting group, or R₃ and R₄, together, are a nitrogen protecting group;

or R₃ and R₄ are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

Z_4 is OX, SX, or $N(X)_2$;

each X is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)R_5$, $C(=O)N(H)R_5$ or $OC(=O)N(H)R_5$;

R_5 is H or C_1-C_8 alkyl;

5 Z_1 , Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or
10 saturated or unsaturated heterocyclic;

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(R_1)(R_2)OR_1$, halo, SR_1 or CN;

15 each q_1 is, independently, an integer from 1 to 10;

each q_2 is, independently, 0 or 1;

q_3 is 0 or an integer from 1 to 10;

q_4 is an integer from 1 to 10;

q_5 is from 0, 1 or 2; and

20 provided that when q_3 is 0, q_4 is greater than 1.

30. The oligomeric compound of claim 23 wherein at least one of L_1 and L_2 is a modified internucleoside linkage.

31. The oligomeric compound of claim 30 wherein at least one of L_1 and at least one of L_2 is a modified internucleoside
25 linkage.

32. The oligomeric compound of claim 30 wherein each L_1 and L_2 is a phosphodiester internucleoside linkage.

33. The oligomeric compound of claim 30 wherein each modified internucleoside linkage is, phosphorodithioate;
30 chiral Sp phosphorothioate; phosphoramidate; thiophosphor-

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amidate; phosphonate; methylene phosphonate; phosphotriesters; thionoalkylphosphonate; thionoalkylphosphotriester; borano-phosphate; boranothiophosphate; thiodiester; thionocarbamate; siloxane; carbamate; sulfamate; morpholino sulfamide;

5 sulfonamide; sulfide; sulfonate; N,N'-dimethylhydrazine; thioformacetal; formacetal; thioketal; ketal; amine (-NH-CH₂-CH₂-); hydroxylamine; hydroxyimine; hydrazinyl; amide (-CH₂-N(JJ)-C(O)-) and (-CH₂-C(O)-N(JJ)-); oxime (-CH₂-O-N=CH-); and alkylphosphorus (-C(JJ)₂-P(=O)(OJJ)-C(JJ)₂-C(JJ)₂-), wherein J

10 is hydrogen or C₁ to C₁₀ alkyl.

34. The oligomeric compound of claim 30 wherein each modified internucleoside linkage is, independently, methyl phosphonate, boranophosphonate, phosphoramidate, 3'-methylenephosphonate or methylene(methylimino).

15 35. The oligomeric compound of claim 23 wherein at least one R₁₄ is L₁ or L₂.

36. The oligomeric compound of claim 23 wherein at least one R₁₄ is L₁ and at least one R₁₄ is L₂.

37. The oligomeric compound of claim 23 comprising from

20 5 to about 50 nucleosides.

38. The oligomeric compound of claim 23 comprising from 8 to about 30 nucleosides.

39. The oligomeric compound of claim 23 comprising from 15 to about 25 nucleosides.

25 40. The oligomeric compound of claim 23 wherein the sum of n and p is from 2 to about 12.

41. The oligomeric compound of claim 23 wherein the sum of n and p is from 2 to about 6.

42. The oligomeric compound of claim 23 wherein the sum of n and p is from 2 to 4.

5 43. A pharmaceutical composition comprising a compound of claim 1 and an acceptable pharmaceutical carrier.

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WHAT IS CLAIMED IS:

1. An oligomeric compound comprising a plurality of covalently-bound nucleosides said oligomeric compound having an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking said internal region wherein said external regions impart nuclease resistance to said oligomeric compound.

2. The oligomeric compound of claim 1 wherein at least
10 one nucleoside in the external regions comprises a substituent
group.

3. The oligomeric compound of claim 2 wherein at least one nucleoside in each of the external regions comprises a substituent group.

15 3. The oligomeric compound of claim 2 wherein each
nucleoside in the external regions comprises a substituent
group.

4. The oligomeric compound of claim 2 wherein each of said substituent groups is covalently bound to the 5', 3' or 2'-position of the sugar moiety of said nucleoside.

5. The oligomeric compound of claim 4 wherein each of said substituent groups is covalently attached to said nucleoside at the 2'-position.

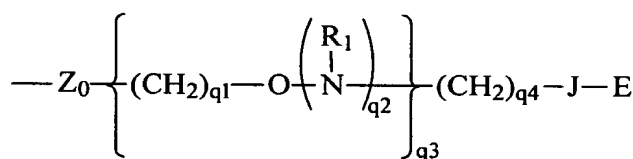
6. The oligomeric compound of claim 4 wherein each of
25 said substituent groups is covalently attached to said
nucleoside at the 5'-position.

7. The oligomeric compound of claim 1 wherein the ribosyl sugar moiety of at least one of said covalently-bound nucleosides in each of said external regions has the L-ribose configuration.

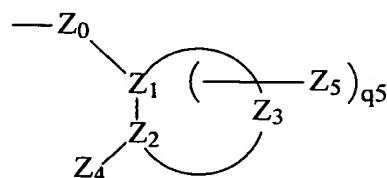
5 8. The oligomeric compound of claim 7 wherein the 5' and 3'-terminal ribosyl sugar moieties of said covalently-bound nucleosides each have the L-ribose configuration.

9. The oligomeric compound of claim 2 wherein each of said substituent groups is, independently, C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₅-C₂₀ aryl, O-alkyl, O-alkenyl, O-alkynyl, O-alkylamino, O-alkylalkoxy, O-alkylaminoalkyl, O-alkyl imidazole, thiol, S-alkyl, S-alkenyl, S-alkynyl, NH-alkyl, NH-alkenyl, NH-alkynyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, N-phthalimido, halogen
10 alkenyl, C₂-C₂₀ alkynyl, C₅-C₂₀ aryl, O-alkyl, O-alkenyl, O-alkynyl, O-alkylamino, O-alkylalkoxy, O-alkylaminoalkyl, O-alkyl imidazole, thiol, S-alkyl, S-alkenyl, S-alkynyl, NH-alkyl, NH-alkenyl, NH-alkynyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, N-phthalimido, halogen
15 keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, heterocycle, carbocycle, polyamine, polyamide, polyalkylene glycol, and polyether;

20 or each substituent group has one of formula I or II:



I



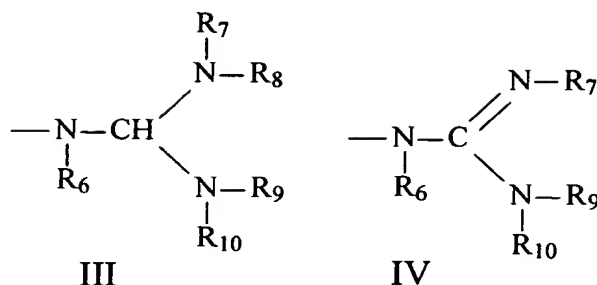
II

wherein:

25 Z₀ is O, S or NH;

J is a single bond, O or C(=O);

E is C₁-C₁₀ alkyl, N(R₁)(R₂), N(R₁)(R₅), N=C(R₁)(R₂), N=C(R₁)(R₅) or has one of formula III or IV;



each R_6 , R_7 , R_8 , R_9 and R_{10} is, independently, hydrogen, $\text{C}(\text{O})\text{R}_{11}$, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{10}$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_{10}$ alkynyl, alkylsulfonyl, arylsulfonyl, a chemical functional group or a conjugate group, wherein the substituent groups are selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl;

or optionally, R_7 and R_8 , together form a phthalimido moiety with the nitrogen atom to which they are attached;

or optionally, R_9 and R_{10} , together form a phthalimido moiety with the nitrogen atom to which they are attached;

each R_{11} is, independently, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, trifluoromethyl, cyanoethoxy, methoxy, ethoxy, t-butoxy, allyloxy, 9-fluorenylmethoxy, 2-(trimethylsilyl)-ethoxy, 2,2,2-trichloroethoxy, benzyloxy, butyryl, isobutyryl, phenyl or aryl;

R_5 is T-L,

T is a bond or a linking moiety;

L is a chemical functional group, a conjugate group or a solid support material;

each R_1 and R_2 is, independently, H, a nitrogen protecting group, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{10}$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_{10}$ alkynyl, wherein said substitution is OR_3 , SR_3 , NH_3^+ , $\text{N}(\text{R}_3)(\text{R}_4)$, guanidino or acyl where said acyl is an acid amide or an ester;

or R₁ and R₂, together, are a nitrogen protecting group or are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

or R_1 , T and L, together, are a chemical functional
5 group;

each R₃ and R₄ is, independently, H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₃ and R₄, together, are a nitrogen protecting group;

or R₃ and R₄ are joined in a ring structure that
10 optionally includes an additional heteroatom selected from N
and O;

$$Z_4 \text{ is } OX, SX, \text{ or } N(X)_2;$$

each X is, independently, H, C₁-C₈ alkyl, C₁-C₈ haloalkyl, C(=NH)N(H)R₅, C(=O)N(H)R₅ or OC(=O)N(H)R₅;

15 R₅ is H or C₁-C₈ alkyl;

Z₁, Z₂ and Z₃ comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;

Z₅ is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, N(R₁)(R₂) OR₁, halo, SR₁ or CN;

each q_1 is, independently, an integer from 1 to 10;

each q_2 is, independently, 0 or 1;

q_3 is 0 or an integer from 1 to 10;

q_4 is an integer from 1 to 10;

30 q_5 is from 0, 1 or 2; and

provided that when q_3 is 0, q_4 is greater than 1.

10. The oligomeric compound of claim 9 wherein said substituent group has formula I, II, III or IV.

11. The oligomeric compound of claim 1 wherein at least one internucleoside linkage in one of said external regions is modified.

12. The oligomeric compound of claim 11 wherein at least
5 one internucleoside linkage in each of said external regions
is modified.

13. The oligomeric compound of claim 11 wherein each of the internucleoside linkages in said external regions are modified.

10 14. The oligomeric compound of claim 11 wherein each modified internucleoside linkage is, independently, methyl phosphonate, boranophosphonate, phosphoramidate, 3'-methylenephosphonate or methylene(methylimino).

15 15. The oligomeric compound of claim 1 wherein at least one internucleoside linkage in one of said external regions is a 2', 5'-internucleoside linkage.

16. The oligomeric compound of claim 15 wherein at least one internucleoside linkage in each of said external regions
20 is a 2', 5'-internucleoside linkage.

17. The oligomeric compound of claim 1 comprising from 5 to about 50 nucleosides.

18. The oligomeric compound of claim 1 comprising from 8 to about 30 nucleosides.

25 19. The oligomeric compound of claim 1 comprising from
15 to about 25 nucleosides.

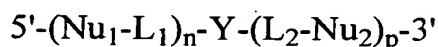
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20. The oligomeric compound of claim 1 wherein each of the external regions comprises from 1 to 6 nucleosides.

21. The oligomeric compound of claim 1 wherein each of the external regions comprise from 1 to 3 nucleosides.

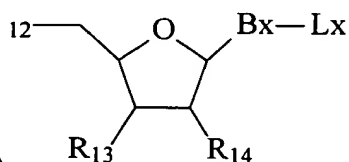
22. A pharmaceutical composition comprising a compound of claim 1 and an acceptable pharmaceutical carrier.

23. An oligomeric compound of the formula:



wherein:

each Nu_1 and Nu_2 , independently, has the formula:



wherein

Bx is a heterocyclic base moiety;

Lx is hydrogen, a protecting group or a substituent group;

one of R_{12} , R_{13} and R_{14} is hydroxyl, a protected hydroxyl, a covalent attachment to a solid support, a nucleoside, an oligonucleoside, a nucleotide, an oligonucleotide, a conjugate group or an optionally protected substituent group;

another of R_{12} , R_{13} and R_{14} is hydrogen, hydroxyl, a protected hydroxyl or an optionally protected substituent group;

the remaining of R_{12} , R_{13} and R_{14} , of Nu_1 , is L_1 ;

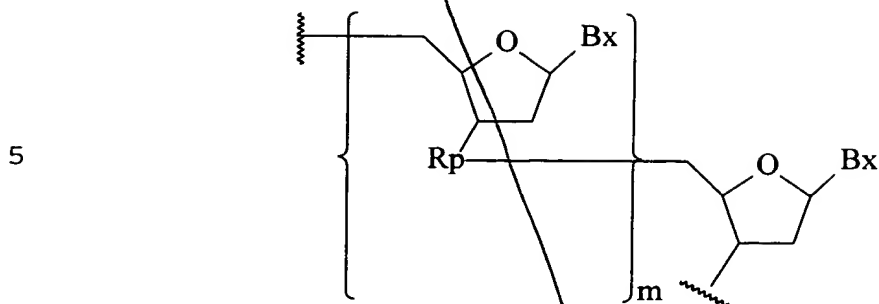
the remaining of R_{12} , R_{13} and R_{14} , of Nu_2 , is L_2 ;

each L_1 and each L_2 is, independently, a phosphodiester internucleoside linkage or a modified internucleoside linkage;

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Y has the formula:



wherein:

each R_p is a chiral R_p phosphorothioate internucleotide linkage; and

10 each n, m and p is, independently, from 1 to 100; where
the sum of n, m and p is from 3 to about 200;

with the proviso that at least one of R_{12} , R_{13} , R_{14} and L_x is a substituent group or at least one of L_1 and L_2 is a modified internucleoside linkage.

15 24. The oligomeric compound of claim 23 wherein at least
one Nu₁ or at least one Nu₂ comprises a substituent group.

25. The oligomeric compound of claim 24 wherein at least one Nu₁ and at least one Nu₂ independently comprise a substituent group.

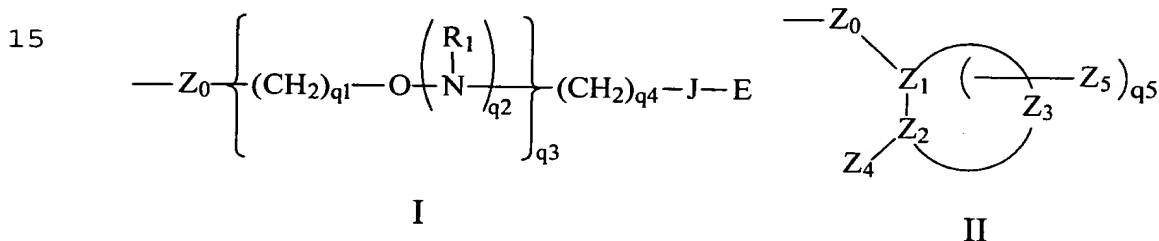
20 26. The oligomeric compound of claim 23 wherein each Nu₁
and each Nu₂ independently comprises a substituent group.

27. The oligomeric compound of claim 24 wherein said substituent group is covalently attached to the 2', 3' or 5'-position of said Nu₁ or Nu₂.

25 28. The oligomeric compound of claim 27 wherein said
substituent group is covalently attached to the 2'-position of
said Nu₁ or Nu₂.

29. The oligomeric compound of claim 23 wherein each of said substituent groups is, independently, C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₅-C₂₀ aryl, O-alkyl, O-alkenyl, O-alkynyl, O-alkylamino, O-alkylalkoxy, O-alkylaminoalkyl, O-alkyl imidazole, thiol, S-alkyl, S-alkenyl, S-alkynyl, NH-alkyl, NH-alkenyl, NH-alkynyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, N-phthalimido, halogen keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, heterocycle, carbocycle, polyamine, polyamide, polyalkylene glycol, and polyether;

or each substituent group has one of formula I or II:

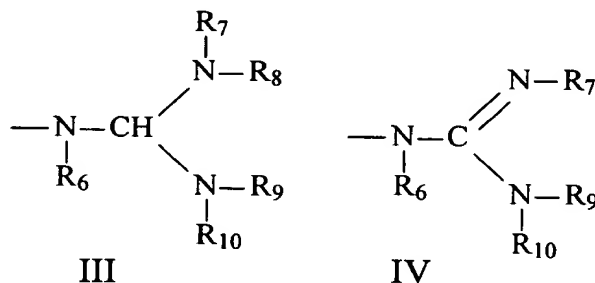


wherein:

Z_0 is O, S or NH;

J is a single bond, C or C(=O);

20 E is C₁-C₁₀ alkyl, N(R₁)(R₂), N(R₁)(R₅), N=C(R₁)(R₂),
N=C(R₁)(R₅) or has one of formula III or IV;



each R_6 , R_7 , R_8 , R_9 and R_{10} is, independently, hydrogen, $C(O)R_{11}$, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl, substituted or unsubstituted

C₂-C₁₀ alkynyl, alkylsulfonyl, arylsulfonyl, a chemical functional group or a conjugate group, wherein the substituent groups are selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl;

or optionally, R₇ and R₈, together form a phthalimido moiety with the nitrogen atom to which they are attached;

or optionally, R₉ and R₁₀, together form a phthalimido moiety with the nitrogen atom to which they are attached;

each R₁₁ is, independently, substituted or unsubstituted C₁-C₁₀ alkyl, trifluoromethyl, cyanoethyloxy, methoxy, ethoxy, t-butoxy, allyloxy, 9-fluorenylmethoxy, 2-(trimethylsilyl)-ethoxy, 2,2,2-trichloroethoxy, benzyloxy, butyryl, isobutyryl, phenyl or aryl;

R₅ is T-L,

T is a bond or a linking moiety;

L is a chemical functional group, a conjugate group or a solid support material;

each R₁ and R₂ is, independently, H, a nitrogen protecting group, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl, substituted or unsubstituted C₂-C₁₀ alkynyl, wherein said substitution is OR₃, SR₃, NH₃⁺, N(R₃)(R₄), guanidino or acyl where said acyl is an acid amide or an ester;

or R₁ and R₂, together, are a nitrogen protecting group or are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

or R₁, T and L, together, are a chemical functional group;

each R₃ and R₄ is, independently, H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₃ and R₄, together, are a nitrogen protecting group;

or R₃ and R₄ are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

$$Z_4 \text{ is } OX, SX, \text{ or } N(X)_2;$$

each X is, independently, H, C₁-C₈ alkyl, C₁-C₈ haloalkyl, C(=NH)N(H)R₅, C(=O)N(H)R₅ or OC(=O)N(H)R₅;

R₅ is H or C₁-C₈ alkyl;

5 Z₁, Z₂ and Z₃ comprise a ring system having from about 4
to about 7 carbon atoms or having from about 3 to about 6
carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms
are selected from oxygen, nitrogen and sulfur and wherein said
ring system is aliphatic, unsaturated aliphatic, aromatic, or
10 saturated or unsaturated heterocyclic;

Z₅ is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, N(R₁)(R₂) OR₁, halo, SR₁ or CN;

15 each q_1 is, independently, an integer from 1 to 10;

each q_2 is, independently, 0 or 1;

q_3 is 0 or an integer from 1 to 10;

q_4 is an integer from 1 to 10;

q_5 is from 0, 1 or 2; and

20 provided that when q_3 is 0, q_4 is greater than 1.

30. The oligomeric compound of claim 23 wherein at least one of L₁ and L₂ is a modified internucleoside linkage.

31. The oligomeric compound of claim 30 wherein at least one of L₁ and at least one of L₂ is a modified internucleoside linkage.

32. The oligomeric compound of claim 30 wherein each L₁ and L₂ is a phosphodiester internucleoside linkage.

33. The oligomeric compound of claim 30 wherein each modified internucleoside linkage is, phosphorodithioate; 30 chiral Sp phosphorothioate; phosphoramidate; thiophosphor-

amidate; phosphonate; methylene phosphonate; phosphotriesters; thionoalkylphosphonate; thionoalkylphosphotriester; boranophosphate; boranothiophosphate; thiodiester; thionocarbamate; siloxane; carbamate; sulfamate; morpholino sulfamide; 5 sulfonamide; sulfide; sulfonate; N,N'-dimethylhydrazine; thioformacetal; formacetal; thioketal; ketal; amine (-NH-CH₂-CH₂-); hydroxylamine; hydroxylimine; hydrazinyl; amide (-CH₂-N(JJ)-C(O)-) and (-CH₂-C(O)-N(JJ)-); oxime (-CH₂-O-N=CH-); and alkylphosphorus (-C(JJ)₂-P(=O)(OJJ)-C(JJ)₂-C(JJ)₂-), wherein J 10 is hydrogen or C₁ to C₁₀ alkyl.

34. The oligomeric compound of claim 30 wherein each modified internucleoside linkage is, independently, methyl phosphonate, boranophosphonate, phosphoramidate, 3'-methylenephosphonate or methylene(methylimino).

15 35. The oligomeric compound of claim 23 wherein at
least one R_{14} is L_1 or L_2 .

36. The oligomeric compound of claim 23 wherein at least one R_{14} is L_1 and at least one R_{14} is L_2 .

37. The oligomeric compound of claim 23 comprising from 20 5 to about 50 nucleosides.

38. The oligomeric compound of claim 23 comprising from 8 to about 30 nucleosides.

39. The oligomeric compound of claim 23 comprising from 15 to about 25 nucleosides.

25 40. The oligomeric compound of claim 23 wherein the sum
of n and p is from 2 to about 12.

